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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/499,526	02/10/00	LU	K CIBT-P01-058

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EXAMINER

DEBERRY, R

ART UNIT

PAPER NUMBER

1647

DATE MAILED:

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/499,526

Applicant(s)

LU ET AL.

Examiner

Regina M. DeBerry

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 June 2001.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 and 15-86 is/are pending in the application.
- 4a) Of the above claim(s) 1-12, 24-27, 34-38, 40-44, 47-49, 52, 55, 56, 61, 62, 64-75, 79-84 and 86 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 13, 15-23, 28-33, 39, 45, 46, 50, 51, 53, 54, 57-60, 63, 76-78 and 85 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-13 and 15-86 ~~are~~ ^{WERE} subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 14 .

- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____ .

U.S. Patent and Trademark Office
PTO-326 (Rev. 04-01)

Office Action Summary

Part of Paper No. 19

Status of Application, Amendments and/or Claims

The Revocation of Prior Powers of Attorney and Appointment of New Power of Attorney or Authorization of Agents has been entered (Paper No. 15, 21 June 2001).

The amendment filed 21 June 2001 (Paper No. 18) is acknowledged.

Claims 1-12, 24-27, 34-38, 40, 41, 44, 47-49, 52 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a nonelected invention(s)/species for the reasons of record.

Claim 14 was cancelled (Paper No. 18).

Claims 42, 43 were withdrawn (Paper No. 18).

Claims 13,15,20,21,23,28-33,39,45,50 were amended (Paper No. 18).

Newly submitted claims 53,54,57-60,63,76-78 and 85 have been added (Paper No. 8).

Newly submitted claims 55,56,61,62,64-75, 79-84,86 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the newly submitted claims are directed to non-elected inventions previously not claimed which include methods of administering islets or cells, methods of administering an organic molecule, method of administering an inhibitor, method of administering to a stem cell. Please see **DETAILED ACTION, Election/Restriction** (Paper No. 7, 14 December 2000). Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 55,56,61,62,64-

75, 79-84, 86 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 13, 15-23, 28-33, 39, 45, 46, 50, 51, 53, 54, 57-60, 63, 76-78, 85 are pending and being acted upon presently.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The objection to claim 29 as set forth at page 4 of the previous Office Action (Paper No. 13, 12 March 2001) is *withdrawn* in view of the amendment (Paper No. 18, 21 June 2001).

The objection of claims 30-32, 39, 42, 43, 50 under 37 CFR 1.75(c) as being improper form as set forth at page 4 of the previous Office Action (Paper No. 13, 12 March 2001) is *withdrawn* in view of the amendment (Paper No. 18, 21 June 2001).

The objection of claims 15 and 46 under 37 CFR 1.75(c) as being improper form as set forth at pages 4-5 of the previous Office Action (Paper No. 13, 12 March 2001) is *withdrawn* in view of the amendment (Paper No. 18, 21 June 2001).

The objection to the specification as set forth at page 5 of the previous Office Action (Paper No. 13, 12 March 2001) is *withdrawn* in view of the amendment (Paper No. 18, 21 June 2001).

The rejection of claims 13-23, 28-32, 39, 42, 43, 50 and 51 under 35 USC 112, second paragraph as set forth at page 10 of the previous Office Action (Paper No. 13, 12 March 2001) is *withdrawn in part* in view of the amendment (Paper No. 18, 21 June

2001). The issue regarding "modifying glucose metabolism" has been resolved. However see section on 35 USC 112, second paragraph below for maintained portions of the rejection.

The rejection of claim 33 under 35 USC 112, second paragraph as set forth at page 10-11 of the previous Office Action (Paper No. 13, 12 March 2001) is *withdrawn* in view of the amendment (Paper No. 18, 21 June 2001).

The rejection of claims 13-20, 22, 30-32, 33, 39, 42, 43, 45, 46, 50 and 51 under 35 USC 112, second paragraph as set forth at page 11 of the previous Office Action (Paper No. 13, 12 March 2001) regarding "pancreatic islet or cell" is *withdrawn* in view of Applicant's convincing argument (Paper No. 18, 21 June 2001).

The rejection of claims 28, 29, 30-32, 39, 42, 43 and 50 under 35 USC 112, second paragraph as set forth at page 11 of the previous Office Action (Paper No. 13, 12 March 2001) regarding claims dependent on a non-elected group is *withdrawn* in view of the amendment (Paper No. 18, 21 June 2001).

The rejection of claims 13, 21, 33 and 45 under 35 USC 112, second paragraph as set forth at page 11 of the previous Office Action (Paper No. 13, 12 March 2001) regarding claims not achieving the goal stated in the preamble is *withdrawn* in view of the amendment (Paper No. 18, 21 June 2001).

The rejection of claims 15, 30, 31, 42, 43 and 50 under 35 USC 112, second paragraph as set forth at pages 11-12 of the previous Office Action (Paper No. 13, 12 March 2001) regarding insufficient antecedent basis is *withdrawn* in view of the amendment (Paper No. 18, 21 June 2001).

35 USC § 112, Second Paragraph

Claims 13, 15-23, 28-33, 39, 45,46,50, 51,53,54,57-60,63,76-78,85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 85 is indefinite in the recitation, the method of any one of the above claims 23, wherein said animal is a human. Claim 85 is indefinite because it is unclear whether claim 85 depends from claim 23 only, claims 13-23, or claims 13-22.

Claim 13, 15-23, 28-33, 39, 45,46,50,51,53,54,57-60,63,76-78,85 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The basis for this rejection regarding "PYY Therapeutic" was set forth at page 10 of the previous Office Action (Paper No.13, 12 March 2001).

Applicant's arguments (page 13-14, Paper No. 18, 21 June 2001) have been fully considered but are not found persuasive for the following reasons.

Applicant states that "the definiteness of claim language must be analyzed, not in a vacuum, but in light of the content of the application and the understanding of one of skill in the art". Applicant further states that "the specification defines the term PYY Therapeutic at page 9, lines 24-25 and ensuing paragraphs provide additional examples that further elaborate the meaning of this term". Lastly, Applicant states that "the specification, such as at page 9, lines 30-34, clearly indicates that although a PYY Therapeutic may be employed in a composition, that it is the agent and not the composition that is the PYY Therapeutic".

The specification states "PYY agonists which can be used as PYY Therapeutics include any compound having the effect of inducing the activity of PYY" (page 6, lines 10-11): "In other embodiments, the PYY Therapeutic is a compound that binds to a PYY receptor such as the PYY Y1 receptor, and mimics (agonist) or inhibits (as an antagonist) the activity for PYY" (page 6, lines 23-25). "In general, the invention relates to methods for regulating (inducing or maintaining) glucose-responsive pancreatic islets or isolated β cells, through the use of a PYY peptide, an analog or derivative of PYY, or an agonist thereof (hereinafter "PYY agonist")". "For ease of reading, both classes of agents are collectively referred to herein as "PYY Therapeutic" (page 9, lines 22-25). The metes and bounds cannot be determined because the term "PYY Therapeutic" includes many different agents, which could **differ** structurally and/or functionally. For example an agonist is included in the broad term "PYY Therapeutic". The specification includes **any compound** in this definition, however the agonist could be an organic compound or it could be an agent that may not have the same activity as the PYY peptide. Applicant's argument does not overcome the rejection.

Claims 21-23, 28-32, 39, 50, amended claims 21, 23 and dependent claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The basis for this rejection regarding "pharmaceutically effective amount" was set forth at page 10 of the previous Office Action (Paper No.13, 12 March 2001).

Applicant's arguments (page 13-14, Paper No. 18, 21 June 2001) have been fully considered but are not found persuasive because the drugs used for treatment can

have multiple effects besides altering the glucose-responsiveness. This rejection, however, can be over come by amending the claims to incorporate "a therapeutically effective amount to induce or enhance the glucose responsiveness..."

Claim Rejections - 35 USC § 112, First Paragraph

Claims 13-23, 28-33, 39, 45, 46, 50, 51, 53, 54, 57-60, 63, 76-78, 85 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for stimulating the ability of fetal islets in culture to respond to glucose by secreting insulin by administering PYY and restoring glucose responsiveness in adult rat islets in culture by administering PYY, does not reasonably provide enablement for the following methods: altering the differentiated state of a pancreatic islet/cell comprising administering to a pancreatic islet/cell a PYY Therapeutic (in vitro or in vivo), modifying glucose metabolism in an animal (or human) or treating a disease associated with altered glucose metabolism comprising administering to an animal (or human) a PYY therapeutic. Furthermore, the specification is enabled for PYY but not "PYY Therapeutic" or any biological equivalent, analog, derivative or variant of PYY. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection was set forth at pages 5-9 of the previous Office Action (Paper No.13, 12 March 2001).

Applicant's arguments (page 11-13 Paper No. 18, 21 June 2001) have been fully considered but are not found persuasive for the following reasons.

Applicant states that as of the filing date, a number of other PYY analogs were available, as indicated by the references and abstracts provided herewith as Exhibit A. Exhibit A is not found persuasive because Exhibit A was not submitted with Applicant's amendment. Applicant states that column 3 of U.S. Patent 5,574,010, incorporated by reference in the specification at the bottom of page 23, points out a number of other references relating to compounds that fall within the scope of the term "PYY Therapeutic". Applicant states that one of ordinary skill in the art using assays described in these references could have identified any number of additional PYY therapeutics using only routine experimentation. Applicant states that a patent need not teach and preferably omits, what is well known in the art. Lastly, Applicant states that the examiner has not cited any relevant art nor relied on any other fact-finding results to rebut the presumption in favor of Applicants. Applicant asserts that the use of PYY Therapeutics is fully enabled by the present specification and the level of skill in the art at the time of filing of the present application.

Contrary to Applicants assertion, the specification is not enabled for PYY Therapeutic. As was stated in the last Office Action, the term "PYY Therapeutic" is not limited to any specific protein, this definition includes many different agents. With just the protein alone, it would require an indeterminate quantity of fundamentally unpredictable investigational experimentation to determine whether any modified polypeptide could be used in the same manner as the native exemplar. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex.

Art Unit: 1647

While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, *Biochemistry* 29:8509-8517; Ngo *et al.*, 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, pp. 492-495). However, Applicant has provided insufficient guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Applicant cites U.S. Patent 5,574,010 as a reference for PYY analogs. This is not found persuasive because the invention claimed in U.S. Patent 5,574,010 is drawn to a method for treating pancreatic tumors which is not predictive to the method claimed in the instant application. The physiology of pancreatic cancer is very different from non glucose-responsive cells.

Applicant is not enabled for a change in differentiation or maturation of pancreatic islet or cells. The specification states that, "the invention comprises methods for inducing islets to express markers indicative of mature islets or for β cells to express

makers indicative of mature β cells by contacting the islets or β cells with a PYY Therapeutic "(page 5, lines 1-6). The specification, however, does not disclose where assays were employed to reveal morphological changes, expression of specific genes or surface markers thus demonstrating that differentiation or maturation has taken place as a result of administering PYY.

Lastly, Applicant is not enabled for modifying glucose metabolism in an animal (or human) or treating a disease associated with altered glucose metabolism comprising administering to an animal (or human) a PYY therapeutic. Applicant cites Exhibit B and Exhibit C to demonstrate that *in vivo* and *in vitro* functions of PYY show a strong correlation. This is not found persuasive because Exhibit B and Exhibit C were not submitted with Applicant's amendment. Furthermore, none of the references cited in the IDS demonstrate the use of PYY to induce or enhance glucose responsiveness of pancreatic islet or cells *in vivo*.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to the same, the absence of working examples directed to maturation and differentiation assays and *in vivo* treatments, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any

Art Unit: 1647

structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Art Unit: 1647

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on Mondays-Fridays 8:00 a.m. - 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 308-2742 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



RMD

August 21, 2001

PHILLIP GAMBEL
PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
724 CENTER 1600
8/22/01